REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 10, 13-16, 18, 31 and 33-37, the only claims pending and currently under examination in this application.

Claims 10 and 31 have been amended to clarify a microarray of distinct selected polypeptides on a slide, wherein each polypeptide is of at least 50 amino acids in length and wherein said microarray comprises 1000 or more discrete regions of distinct selected polypeptide per cm^2 of slide, and wherein discrete regions have a diameter of from 20 to 200 µm. Support for this amendment can be found in the specification on page 3, lines 17-18 as an exemplary location.

As no new matter has been added by way of these amendments, entry thereof by the Examiner is respectfully requested.

Claim Rejections – 35 USC § 102

The Examiner rejects Claims 31 and 33-37 under 35 U.S.C. § 102(e) as being anticipated by Winkler et al. Applicants respectfully submit that the presently claimed invention is not anticipated by the cited reference.

In the previous response and reiterated herein, the Applicants note that Winkler *et al.* is directed to methods of synthesizing polymers *in situ* on a substrate, or to the use of non-planar substrates, and thus does not teach the invention set forth in Claims 31 and 33-37.

As the methods of Winkler *et al.* are designed for the synthesis of polymers on a substrate, they can not be adapted to provide the microarrays taught by Applicants. As was previously discussed by Applicants' response of June 11, 2002, distinct, selected polypeptides of at least 50 amino acids in length cannot be synthesized *in situ* to provide for a homogeneous spot of a single peptide. The research article Fodor *et al* (*Science* 251:767-773, 1991), previously provided, describes the method of reacting monomers on a substrate surface to generate polymers. The Fodor paper shows light directed synthesis of two pentapeptides YGGFL and PGGFL on the surface of a substrate, shows that the peptides have been correctly synthesized, and further shows a ten-step binary synthesis of peptides of a range of sizes, up to 10 amino acids in length.

Fodor, on page 771, second paragraph of the first column states: "The net coupling yield *per cycle* in these experiments is typically between 85 and 95 percent." and further recites, in reference 9, the rigorous methods that were used to derived these figures. Therefore, each time

a residue is added to a growing polypeptide chain using this method, it is added with an efficiency of 85-95%.

For the purposes of the following discussion, it will be assumed that the coupling efficiency of each cycle is 90%, the average of 85% and 95%. Using the above information, simple algebra teaches that the synthesis of a polypeptide using these methods becomes less and less efficient. For example, assuming the first amino acid is coupled to the substrate is 100% efficient, the synthesis of a two-mer polypeptide will be 90% efficient, the synthesis of a four-mer polypeptide will be 73% (0.9 x 0.9 x 0.9), the synthesis of a 10-mer polypeptide will be 34% (i.e. 0.9^9), the synthesis of a 20-mer polypeptide will be 13% (i.e. 0.9^{19}) efficient, the synthesis of a 35-mer polypeptide will be 2.5% (i.e. 0.9^{34}) efficient, and the synthesis of a 50-mer polypeptide will be 0.5% (i.e. 0.9^{49}) efficient. Thus, using an average of 90% coupling efficiency, if a 50-mer is synthesized using the in situ synthesis method, only 0.5% of the polypeptides will have the correct sequence. In other words, synthesis of a 50-mer using this method will result in a heterogeneous mixture of polypeptides, only 5 molecules in a 1000 of which will have the correct sequence.

At this level of inaccuracy, the method ceases to be functional, and is no longer useful for synthesizing a selected polypeptide onto a substrate. This effect is demonstrated in the Fodor paper, in which it is noted that no polypeptide of over 7 residues in length was highly bound by a specific antibody (page 771, second column, second paragraph), despite at least one of the polypeptides having a sequence that should have bound to the antibody. As was previously discussed by Applicants' response of June 11, 2002, polypeptides of at least 50 amino acids in length cannot be synthesized *in situ* to provide for a homogeneous spot of a selected peptide as claimed.

In response to arguments made and herein reiterated by Applicants, the Examiner asserts that they are not persuasive because the present "claims are drawn to a microarray having polypeptides of at least 50 amino acids", adding that the "claims do not define or limit the sequence of the polypeptides such that the "correct sequence" is provided. Applicants respectfully submit that the present claims are directed to a microarray of discrete selected polypeptides on a slide, wherein each polypeptide is of at least 50 amino acids in length and wherein said microarray comprises 1000 or more discrete regions of distinct selected polypeptide per cm^2 of slide, and wherein discrete regions have a diameter of from 20 to 200 μm.

The Applicants note that, without exception, the claims as amended refer to the use of a distinct, selected polypeptide, and that each spot on the microarrays as claimed therefore refers to specific polypeptide that has been selected for deposition on the array. In contrast, the methods of Winkeler *et al.* cannot provide for a selected polypeptide, because the method of synthesis results in a random aggregation of polypeptides having errors in synthesis. Although the claims as amended are indeed drawn to a product, in the present case, particular structural limitations of that product naturally flow from the process by which it is made, and from the physical limitations of such methods. In all cases, the microarrays as claimed employ selected polypeptides at the beginning of the process of assembly, and therefore the product as claimed consists in all cases of discrete regions of distinct, selected polypeptides.

MPEP § 2131 states:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

As discussed above, the method of Winkler et al., which is drawn to the *in situ* synthesis of polypeptides and oligonucleotides with diverse sequences, is incapable of producing discrete spots on an array containing a distinct, selected polypeptide of at least 50 amino acids, nor, indeed, of producing peptides of this length which even approach homogeneity. As such, Winkler et al. fails to teach this element of the method as claimed. Accordingly, the withdrawal of this rejection is respectfully requested.

The Examiner rejects Claims 10, 13-15, 18, 31 and 33-37 under 35 U.S.C. § 102(e) as being anticipated by Barrett et al. Applicants respectfully submit that the presently claimed invention is not anticipated by the cited reference.

With regard both to Claims 10 and 31, the Examiner states that "Barrett et al. disclose a microarray of discrete polypeptides on a slide (Column 8, lines 15-20) wherein each polypeptide is at least 50 amino acids (e.g. antibody, Abstract), wherein the microarray comprises 1000 or more discrete regions of polypeptide/cm^2 wherein the regions have a diameter or 20 to 200 μm (Column 18, line 67-Column 19, line 4 and Column 19, line 66-Column 20, line 68)."

For convenience, the text of the cited sections of the patent are reproduced below.

for a site on the surface, are illustrated by the following reactions:

$$S_f—X—B—SBS—AL_f—L'+L \rightarrow S_f—X—B—SB-S—AL_f—L+L' \quad (1).$$

$$S_f—X—B—SBS—AL_f+L/L' \rightarrow S_f—X—B—SB-S—AL_f—L'+L \quad (2).$$

The presence of target ligand can be determined by analyzing appropriately for the loss or buildup of label on the predefined regions of the surface.

III. Substrate Preparation

Essentially, any conceivable solid substrate may be employed in the invention. The substrate may be biological, nonbiological, organic, inorganic, or a combination of any of these, existing as particles, strands, precipitates, gels, sheets, tubing, spheres, containers, capillaries, pads, slices, films, plates, slides, etc. The substrate may have any convenient shape, such as a disc, square,

TABLE 3

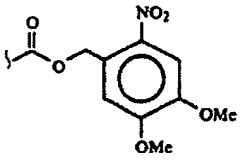
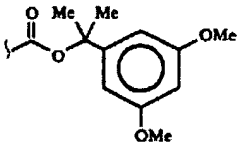
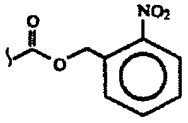
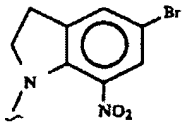
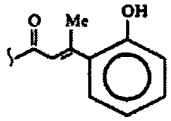
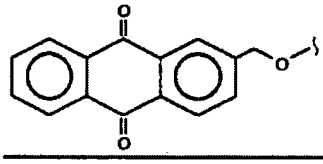
Example Protecting Groups	Name
	6-nitroveratryloxy-carbonyl (NVOC)
	dimethyldimethoxy-benzyloxycarbonyl (DDZ)
	nitrobenzyloxy-carbonyl (NBOC)
	5-bromo-7-nitroindolinyl (BNI)
	O-hydroxy-α-methyl-cinnamoyl (HMC)
	2-oxymethylene anthraquinone (OMA)

TABLE 4

Example protecting groups and their deprotection wavelengths

Group	Deprotection Wavelength
Nitroveratryloxycarbonyl	UV (300-350 nm)
Nitrobenzyloxycarbonyl	UV (300-350 nm)
Dimethyldimethoxybenzyloxycarbonyl	UV (280-300 nm)
5-Bromo-7-nitroindolinyl	UV (420 nm)
o-Hydroxy-α-methyl cinnamoyl	UV (300-350 nm)
2-Oxymethylene anthraquinone	UV (350 nm)

B. Irradiation

Once the surface is covered with a plurality of caged binding members, selected regions of the surface may be irradiated to provide activated binding members predefined regions of the surface may be selectively activated by electron beam lithography, ion beam lithography, X-ray lithography, or any other radiation method. In a preferred embodiment, the radiation is UV, near IR, or visible light. The light source may be coherent or non-coherent. The protective group may alternatively be an electrochemically-sensitive group which may be removed in the presence of an electric current.

In some embodiments, the exposed area is less than about 1 cm^2 or less than about 1 mm^2. In preferred

embodiments the exposed area is less than about 10,000 μm^2 or, more preferably, less than about 100 μm^2. Spaces between activated regions are not critical and will generally be greater than about 1 μm.

In a preferred embodiment, a surface provided with a plurality of sites occupied by photosensitive N-deriva-

tives of biotin or biotin analogs is exposed to a desired light pattern to cause loss of some or all of the photosensitive protecting groups at predefined regions on the surface. Such irradiation of the N-derivatized biotin compounds of the present invention leads to formation of surface-bound biotin or biotin analogs having a strong specific binding affinity for avidin or avidin analogs. The specific binding affinity of biotin and avidin is one of the strongest known between macromolecules ($K_a = 10^{15}\ M^{-1}$). This binding persists when the carboxyl terminus of biotin is attached to another entity, e.g., a surface, or when avidin is attached to another molecule. Avidin possesses four subunits having specific binding affinity for biotin molecules. For example, deprotected biotin sites may be incubated with avidin or an avidin conjugate of an anti-ligand, e.g., an antibody, to provide a localized concentration of the desired anti-ligand on the surface. When incubation with avidin alone is performed, it is necessary to further incubate the resulting product with a preselected species having specific binding affinity for avidin, e.g., a biotinylated anti-ligand. Thus, biotinylated anti-ligands can be bound to the free sites of avidin to afford anti-ligands immobilized at predefined regions on the surface. For a general discussion of the use of the biotin-avidin interaction in molecular biology, see Bayer, et al. Once localization of the anti-ligand is complete, the light pattern can be changed and the same or a different anti-ligand can be localized at other discrete sites on the surface.

V. Attachment of Anti-ligands

An anti-ligand is one or more molecules that recognize a particular ligand in solution. Examples of ligands that can be investigated by this invention include, but are not restricted to agonists and antagonists for cell membrane receptors, toxins and venoms, viral epitopes, antigenic determinants, hormones, hormone receptors, steroids, peptides, enzymes, substrates, cofactors, drugs, lectins, sugars, oligonucleotides, oligosaccharides, proteins, and monoclonal and polyclonal antibodies.

Anti-ligands that mediate a biological function on binding with particular ligand(s) are of most interest Suitable anti-ligands include relatively small, single molecules, such as cofactors, which show specific binding properties. Typically, anti-ligands will be greater than about 100 daltons in size and more typically will be greater than about 1kD in size. Other examples of anti-ligands include, but are not restricted to, the common class of receptors associated with the surface membrane of cells and include, for instance, the immunologically important receptors of B-cells, T-cells, macrophages and the like. Other examples of anti-ligands that can be investigated by this invention include but are not restricted to hormone receptors, hormones, drugs, cellular receptors, membrane transport proteins, steroids, peptides, enzymes, substrates, cofactors, vitamins, lectins, sugars, oligonucleotides, oligosaccharides, viral epitopes, antigenic determinants, glycoproteins, and immunoglobulins, e.g., monoclonal and polyclonal antibodies.

In a preferred embodiment, the anti-ligand will be a biotinylated receptor which binds specifically to avidin. Many biotinylated anti-ligands and biotinylating reagents are commercially available. (See, for example, *Vector Laboratories, Inc., Catalog*, Burlingame, CA) Methods for biotinylating desired anti-ligands are well-known in the art and are described, for example, at Bayer, et al.

Applicants respectfully submit that, notwithstanding the Examiner's citation, Barrett et al. nowhere teach that the microarray comprises 1000 or more discrete regions of distinct polypeptide per cm^2 of slide. Indeed, the Applicants note that Barrett *et al.* are silent with regard to numerous structural aspects of a microarray beyond description of the individual exposed areas and their contents, the term "microarray" itself being entirely absent from the cited reference as is any discussion of the density of array spots. The Applicants additionally note that Barrett *et al.* fail to teach a cationic film on a solid support capable of binding peptide, as claimed. It is well known that to support a claim of anticipation under 35 U.S.C. § 102(e), each and every element of the invention as claimed must be taught. Since Barrett et al. fail to teach each and every element of the claimed invention, Claims 10, 13-15, 18, 31 and 33-37 are not anticipated under 35 U.S.C. § 102(e) by Barrett et al. and this rejection may be withdrawn.

Claim Rejections – 35 USC § 103

The Examiner rejects Claims 10, 13-15, 18, 31, 33-35 under 35 U.S.C. § 103(a) as being unpatentable over Beattie (U.S. Patent No. 5,843,767, filed 10 April 1996) as defined by Zubay, G. (Biochemistry,3r+d. Wm C. Brown Pub., Dubuque Iowa, 1993, pages 964-966) in view of Chang (U.S. Patent No. 4,829,010, filed May 9 1989). Applicants respectfully submit that the presently claimed invention is not made obvious by the cited combination of references.

In the previous response, and reiterated herein, Applicants note that the rejected claims recite that the microarray is created by loading an aqueous solution of a selected polypeptide of at least 50 amino acids in length in a reagent-dispensing device having an elongate capillary channel adapted to hold a quantity of the reagent solution and having a tip region at which the solution in the channel forms a meniscus, and tapping the tip of the dispensing device against a surface of a planar solid support at a defined position, with an impulse effective to break the meniscus in the capillary channel and deposit a selected volume between 0.002 and 2 nl of solution on the surface of the planar solid support such that it forms discrete regions with a diameter from 20-200 μm. The cited art fails to teach an array created by the methods of the invention, and fail to teach an array having the specific geometry set forth by applicants.

Applicants note that the substrate of Beattie is not a solid planar surface, but a substrate comprising "a multiplicity of discrete channels", and where the binding reagent is not on the flat surface but on the walls of the channels, which are curved surfaces. As stated by Beattie, a "variety of materials can be immobilized or fixed to the glass surfaces within the channels of the

NCG array, to yield a high surface area to volume ratio ", which is not found in a planar surface. The methods of Beattie et al. cannot teach a planar array having a defined diameter, because the arrays of Beattie et al. are immobilized or fixed to the channel walls, and thus are not a planar region.

Further, the microfluidic devices utilized in the methods of Beattie et al. do not deliver fluids by the tapping and deposition method recited in the present claims, but with a microfluidic jet (col. 14, lines 32-35). Such micro-jet devices operate by a different mechanism, and are not expected to generate the same array on a planar surface as arrays produced by the methods of the present invention. In fact, the methods of Beattie et al. utilize a flow-through vacuum system for binding DNA probes or targets (example 6), a modification that is not possible where the substrate is a non-porous slide. Because the microfluidic devices of Beattie et al. are utilized with a porous substrate, not a solid slide, one of skill in the art is not motivated to combine the microfluidic device with the teachings of Chang in order to achieve the presently claimed invention.

Beattie et al. specifically teaches away from the use of flat, i.e. planar, substrates, stating that:

> "Another limitation of these prior art approaches is the fact that a flat surface design introduces a rate-limiting step in the hybridization reaction, i.e., diffusion of target molecules over relatively long distances before encountering the complementary probes on the surface. In contrast, the microfabricated apparatus according to the present invention is designed to overcome the inherent limitations in current solid phase hybridization materials, eliminating the diffusion-limited step in flat surface hybridizations and increasing the cross sectional density of DNA. "

The Office Action states that Beattie et al. teaches the use of a slide. Applicants respectfully disagree. Beattie et al. is clearly and resolutely directed to the use of a porous material having functional wells. The citation to Beattie in the Office Action reads as follows:

> Initial lamination process development is carried out using unablated polymeric material (or alternatively using glass slides and/or silicon wafers). Cure temperature, pressure and fixturing are optimized during this process development. Thereafter, the optimized processing parameters are employed to laminate both nonporous wafers and polymeric arrays. The final lamination is done such that the alignment of the two layers creates functional wells.

One of skill in the art, upon reading the specification of Beattie et al., can be in no doubt that the reference does not intend arrays to be produced on a flat surface, but rather on a microfabricated apparatus having numerous channels for binding of the DNA. Applicants

respectfully submit that Beattie et al. does not teach microarrays on a slide – only that the arrays of the Beattie invention could utilize a slide in initial fabrication prior to creation of the wells that are central to the Beattie invention. Indeed, one need only read the title of the patent, "Microfabricated, Flowthrough Porous Apparatus for Discrete Detection of Binding Reactions" to understand that Beattie et al. does not teach microarrays on slides, but rather on a flow-through porous apparatus.

Beattie et al. does not – indeed, cannot - teach the dimensions of discrete regions taught by Applicants and specifically recited in the rejected claims, because Beattie et al. does not teach a planar array, but rather an array where the sides of wells are coated with DNA.

Further, with respect to Claims 10, 13-15 and 18, Beattie et al. cannot teach a product produced by a method wherein a dispensing device taps the surface of a planar solid, since the substrate of Beattie et al. comprises wells, (i.e. an open space). It would thus be physically impossible to utilize the teachings of Beattie to thereby derive a device whose production necessitates tapping the tip of the dispensing device against a surface of a planar solid support at a defined position.

Applicants respectfully submit that there is no reason to combine the teachings of Chang, which may utilize a slide, with the teachings of Beattie et al., which specifically teach that a flat surface design is undesirable as shown above. The combination of the two references is clearly a case of hindsight – picking and choosing from disparate elements in order to spin together Applicants' invention, where the references themselves clearly do not suggest being combined.

One of skill in the art would read Beattie et al. as teaching a particular flow-through apparatus, in which a solution is sprayed into a well in order to provide a greater surface area for binding. Such teachings are not reasonably combined with the pipetting device of Chang et al.

In response to arguments presented by Applicants and reiterated herein, the Examiner maintains the reasoning that "Beattie et al specifically teach a slide (Column 11, lines 40-42). While the reference does create nanoporous wells within the substrate, the substrate is a slide and therefore encompassed by the claimed 'slide'" (Office Action page 9).

Applicants note that the use of the term "slide" in the reference cited by the Examiner clearly substantiates the use of hindsight in making this determination of obviousness. The full context of the term cited from Beattie et al. is as below:

Part B: Ablation tooling and processing

[0090] Contact mask excimer laser machining is a preferred processing technique because it is a lower cost technique than projection mask excimer laser machining. A projection mask is, however, employed when the feature size less than 50 .mu.m. One or more masks with a variety of pattern sizes and shapes are fabricated, along with fixtures to hold the mask and material to be ablated. These masks are employed to determine the optimal material for laser machining and the optimal machining conditions (i.e., mask hole size, energy density, input rate, etc.). Scanning electron microscopy and optical microscopy are used to inspect the excimer laser machined parts, and to quantify the dimensions obtained, including the variation in the dimensions.

[0091] In addition to ablating the sample wells into the polymeric material, the adhesive material is also ablated. This second ablation is undertaken so that the diameter of the hole in the adhesive is made larger than diameter of the sample well on the adhesive side of the polymeric material. This prevents the adhesive from spreading into the sample well and/or the nanoporous glass during lamination.

[0092] Part C: Lamination tooling and processing

[0093] Initial lamination process development is carried out using unablated polymeric material (or alternatively, using glass slides and/or silicon wafers). Cure temperature, pressure, and fixturing are optimized during this process development. Thereafter, the optimized processing parameters are employed to laminate both nanoporous wafers and polymeric arrays. The final lamination is done such that the alignment of the two layers creates functional wells.

Applicants note that this is the only use of the term "slide" in the entirety of the reference, and it is used to denote one of the materials, among several of which could be chosen, to which function may be imparted in order to arrive at the product claimed by Beattie et al. The process taught by Beattie et al., at its completion, "creates functional wells" for a flowthrough capacity whose presence is required and in every case taught by Beattie et al. The Abstract of the cited reference indicates that, "The apparatus is characterized by discrete and isolated regions that extend through said substrate and terminate on a second surface thereof such that when a test sample is allowed to the substrate, it is capable of penetrating through each such region during the course of said binding reaction." It is thereby made plain to one of skill in the art that the device taught by Beattie et al. absolutely requires the presence of channels through the substrate, be it glass or silicon, in order to function. As discussed above, it is equally plain that the substrate taught by Beattie et al. cannot be functionally combined with a reference teaching the binding of polypeptides to a planar surface, as the described product cannot function without

wells which penetrate the substrate to allow flowthrough. A combination of references which results in an inoperable reference teaches away from that combination, supporting a showing of nonobviousness of the invention under examination. See *In re* Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

Accordingly, the Examiner's argument that "the substrate [of Beattie et al.] is a slide and therefore encompassed by the claimed 'slide'" is without force. As discussed above, a substrate can have ablative polypeptide binding surfaces which penetrate and extend through it, thereby enabling the function of the product of Beattie et al. exclusively, or a substrate can present a planar surface upon which discrete regions of polypeptide with a particular defined diameter can be deposited, thereby enabling the function of the presently claimed invention exclusively. These conditions being mutually exclusive of one another, they cannot both be encompassed by a claim drawn to a "slide" in the presence of other relevant limitations as discussed. Applying the Examiner's logic, the claims of the present application would then be considered to infringe upon any patent wherein the use of a slide is taught for any purpose, or even to encompass a product consisting solely of a blank glass slide itself. As this is not the case, it is difficult at best to see the merits of the argument as presented in the Office Action.

The Examiner additionally states, without providing citation, that "Applicant asserts that the method used by Beattie differs from the method of Claim 10," and that this is not persuasive because the process of making the product does not define it over the prior art.

Applicants have at no point in any communication sought to distinguish the claimed product over the prior art by distinguishing its method of production except where this is specifically relevant to the structure of the claimed product. The product as claimed is physically described by the method used to produce it, with resulting limitations upon the product itself. One argument made by Applicants highlights the fact that a product of Claim 10 cannot result from the teachings of Beattie et al. as it would be physically impossible to utilize those teachings to arrive at a device whose method of production involves tapping the tip of the dispensing device against a surface of a planar solid support at a defined position, since the substrate of Beattie et al. comprises wells (i.e. an open space).

In response to Applicants' argument that one of skill in the art would not reasonably combine the porous substrate of Beattie et al. with the pipetting device of Chang, the Examiner states that the art is analogous. The Applicants note, however, that the fact that the device of both references involves the immobilized binding of polymers does not remedy the structural differences which render these teachings unable to be operatively combined. The inkjet method

employed by Beattie et al. and cited by the Examiner is indeed, as argued by the Applicants, a non-impact, contactless method of solution dispensing which is accurately described by Applicants as "spraying" and thereby contrasted with the pipetting method as employed by Chang. While both methods do indeed find uses in broadly analogous art, the structural divergence, namely that of incorporating a porous versus a planar surface, of the respective products renders the combination of the pipetting method of Chang and the substrate of Beattie et al. inoperable and substantiates the nonobviousness of the presently claimed invention.

Because Beattie et al. and Chang are silent with regard to loading a polypeptide solution into an elongate capillary channel and tapping its tip onto the support to dispense the solution therein in a precise amount and pattern, the Examiner seeks to base the previously made rejections upon the judicial precedent of *In re* Best (195 USPQ 430) and *In re* Fitzgerald (205 USPQ 594). However, the facts of *In re* Fitzgerald themselves illustrate precisely why the application of this precedent is invalid in the present case. According to MPEP section 2112:

> In *In re* Fitzgerald et al., 205 USPQ 594 (CCPA 1980), the claims were directed to a self-locking screw-threaded fastener comprising a metallic threaded fastener having patches of crystallizable thermoplastic bonded thereto. The claim further specified that the thermoplastic had a reduced degree of crystallization shrinkage. The specification disclosed that the locking fastener was made by heating the metal fastener to melt a thermoplastic blank which is pressed against the metal. After the thermoplastic adheres to the metal fastener, the end product is cooled by quenching in water. The examiner made a rejection based on a U.S. patent to Barnes. Barnes taught a self-locking fastener in which the patch of thermoplastic was made by depositing thermoplastic powder on a metallic fastener which was then heated. The end product was cooled in ambient air, by cooling air or by contacting the fastener with a water trough. The court first noted that the two fasteners were identical or only slightly different from each other. "Both fasteners possess the same utility, employ the same crystallizable polymer (nylon 11), and have an adherent plastic patch formed by melting and then cooling the polymer." Id. at 596 n.1. The court then noted that the Board had found that Barnes' cooling rate could reasonably be expected to result in a polymer possessing the claimed crystallization shrinkage rate. Applicant had not rebutted this finding with evidence that the shrinkage rate was indeed different. They had only argued that the crystallization shrinkage rate was dependent on the cool down rate and that the cool down rate of Barnes was much slower than theirs. Because a difference in the cool down rate does not necessarily result in a difference in shrinkage, objective evidence was required to rebut the 35 U.S.C. 102/103 prima facie case.

Thus, in *In re* Fitzgerald, the invention under examination was met by a single reference in which an identical or near-identical product possessing the same utility was judged to be produced by a method with an inherent capacity to produce an object indistinguishable from the product under examination. In contrast, the present application is met by two references defined by a third, none of which teaches a product with either the same utility or structure as that of the invention as claimed. It is, at best, unclear what the "inherent" properties of a product combining the references of Beattie et al. and Chang might be and equally unclear how these would relate

to any properties of the presently claimed invention given that, as discussed above, the substrate of Beattie et al. is porous and designed to accommodate flowthrough, the solution deposition method of Beattie is a non-impact method, the density of the array matrix of Chang is dependent on its function as an immunoadsorbent of cells, and the solution deposition mechanism of Chang is incapable of producing the array density specified in the present claims.

Therefore the Applicants respectfully submit that, unlike the situation presented in *In re* Best, the Examiner has not set forth "reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art." Accordingly, the Examiner is not in a position to invoke the above-quoted rule of law enunciated in Best and cases cited therein. Simply stated, it is not enough to assert that a set of prior art references which contain no motivation to combine can together inherently embody every novel aspect of the invention under examination and, based on that assertion alone, shift the burden of persuasion to the Applicants to establish that these elements are absent from a speculative combination assembled from hindsight. See *In re* Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968). On this record, the Examiner cannot require the Applicants "to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on."

As such, the Applicants respectfully submit that the presently claimed invention is not taught or suggested by the cited combination of references. In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 16 and 36 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie as defined by Zubay in view of Chang as applied above, and further in view of Van Ness et al. Van Ness et al. specifically teach a cationic film for convenient attachment of polypeptides.

In the prior response and reiterated herein, Applicants respectfully submit that the secondary reference does not correct the deficiencies of the primary reference. Van Ness et al. fails to teach or suggest a planar microarray on a slide comprising at least 1000 different polypeptides/cm^2, and wherein discrete regions have a diameter of from 20 to 200 μm. As described above, one of skill in the art would not reasonably combine the teachings of Beattie et al., which require a flow-through apparatus, with the teachings of Chang et al., which provide for a low-density planar array. Van Ness et al. fail to remedy the deficiencies of the primary

references. Van Ness et al. teach particular coatings, but not their use in the preparation of a microarray according to the presently claimed invention.

In response to arguments presented by Applicants and reiterated herein, the Examiner states that they are not found persuasive to overcome the above rejection for the reasons stated above regarding Beattie and Chang. As these reasons have been addressed above, the Applicants respectfully submit that the cited combination of references does not make obvious the presently claimed invention and request withdrawal of the rejection.

Claims 16 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barrett et al. (U.S. Patent No. 5,353,743, filed 13 November 1990) in view of Van Ness et al. (U.S. Patent No. 5,667,976, filed 14 February 1996). In making this rejection, the Examiner has asserted that Barrett et al. teaches all of the elements of the claimed invention but for a cationic film, for which element the Examiner looks to Van Ness et al.

As discussed above, notwithstanding the Examiner's citation, Barrett et al. nowhere teach that the microarray comprises 1000 or more discrete regions of distinct polypeptide per cm^2 of slide. Indeed, the Applicants note that Barrett et al. are silent with regard to numerous structural aspects of a microarray beyond description of the individual exposed areas and their contents, the term "microarray" itself being entirely absent from the cited reference as is any discussion of the density of array spots.

Barrett et al. therefore fail to teach or suggest a microarray of discrete polypeptides on a slide wherein each polypeptide is at least 50 amino acids, wherein the microarray comprises 1000 or more discrete regions of polypeptide/cm^2 and wherein the regions have a diameter of 20 to 200 μm. Since Van Ness et al. was cited solely for the cationic film element, it fails to remedy this deficiency in Barrett et al.

Accordingly, Barrett et al. in view of Van Ness et al. fails to teach or suggest all of the elements of the claimed invention. As such, Claims 16 and 36 are not obvious under 35 U.S.C. § 103(a) over Barrett et al. in view of Van Ness et al. and this rejection may be withdrawn.

CONCLUSION

In view of the amendments and remarks above, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-128.

Respectfully submitted,

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